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Optically Active Amines. XII.[1] Synthesis and Spectral Properties of Some Optically Active α-Oximino Ketones and α-Amino Ketone Hydrochlorides. Dimerization of α-Amino Ketones[2]

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A number of α-oximino ketones, some with a steroidal carbon skeleton, were prepared. On the basis of their uv (isotropic absorption) spectra, they are assigned the anti oximino configuration. Their CD spectra in ethanol show a maximum near 340 nm associated with the carbonyl n → π* transition. This maximum is similar in sign and magnitude to that of a cisoid α,β-unsaturated ketone of the same chirality. A second maximum near 270 nm is tentatively assigned to the nitrogen n → π* transition. In 1 *N* ethanolic potassium hydroxide, CD maxima are observed for n → π* and π → π* transitions. The α-oximino ketones were reduced to the α-amino ketone hydrochlorides in ethanolic hydrogen chloride with hydrogen over a palladium catalyst. The CD spectra of the α-amino ketone hydrochlorides are interpreted on the basis of an antioctant contribution of the ammonium group. Treatment of the hydrochlorides of 3-amino-4-methyl-2-pentanone, 2-aminocyclopentanone, 2-aminocyclohexanone, 2α-amino-5α-androstan-17β-ol-3-one, (1*R*,3*S*)-3-amino-2-bornanone, and 16β-amino-5α-androstan-3α- and -3β-ol-17-one with bases causes the formation of the corresponding α-amino ketones. The latter condense to tautomeric mixtures of the dihydropyrazines. Only 16β-amino-5α-androstan-3α- and -3β-ol-17-one could be isolated free of the dihydropyrazines. Dihydropyrazines with alkyl or cyclohexano substituents are oxidized by air to the corresponding pyrazines. Attempts to oxidize the mixture of dihydropyrazines formed from 16β-amino-5α-androstan-3α-ol-17-one with hydrogen peroxide in aqueous potassium hydroxide gave only the *seco*-16,17-dioic acid. The dihydropyrazines formed by dimerization of (1*R*,3*S*)-3-amino-2-bornanone were oxidized in dioxane–water with sulfuric acid–sodium nitrite, and di[(1*R*)-bornano][2,3-*b*:2′,3′-*e*]pyrazine was isolated. Most of the steroidal α-oximino ketones and α-amino ketone hydrochlorides show no endocrine activity. 2α-Amino-5α-androstan-17β-ol-3-one hydrochloride has moderate antiuterotropic activity, but it is toxic.

In connection with our continuing interest in the stereochemistry and spectral properties of optically active amines,[1] we undertook the synthesis of a number of optically active primary α-amino ketones, for the most part those having a steroidal skeleton.

Although 16ξ-amino-5-androsten-3β-ol-17-one has been reported without characterization,[4] other steroidal primary α-amino ketones prepared earlier[5-7] have the amino group at a tertiary carbon atom in a sterically hindered environment.[5] The amino group is resistant toward futher reaction such as N substitution or dimerization to the corresponding dihydropyrazine.[8] Steroidal primary α-amino ketones with the amino group on a secondary carbon atom would be more reactive and might possess unusual biological properties. If the optically active α-amino ketones dimerize, oxidation of the resulting mixture of dihydropyrazines[8,9] would lead to a group of optically active pyrazines.

The successful reduction of α-oximino ketones in ethanolic hydrogen chloride with hydrogen over a palladium catalyst to α-amino ketone hydrochlorides[10] suggested the use of steroidal α-oximino ketones for the preparation of steroidal α-amino ketones having the amino group on a secondary carbon atom.

We now record the synthesis of a number of steroidal α-oximino ketones as well as a number of model compounds (Chart I) by way of the nitrosation of the corresponding ketones.[11] Most of these α-oximino ketones were reduced to the corresponding α-amino ketone hydrochlorides. On treatment with bases, the latter dimerize to a tautomeric mixture of the corresponding dihydropyrazines. Oxidation of some of the dihydropyrazines affords the respective pyrazines **11–15**.

(1) Paper XI: H. E. Smith and T. C. Willis, *J. Amer. Chem. Soc.*, **93**, 2282 (1971).

(2) Taken from the Ph.D. Dissertation of A. A. H., Vanderbilt University, Jan 1970. A preliminary report has appeared: H. E. Smith and A. A. Hicks, *Chem. Commun.*, 1112 (1970).

(3) NIH Predoctoral Fellow, 1967–1969.

(4) A. Hassner and A. W. Coulter, *Steroids*, **4**, 281 (1964).

(5) D. F. Morrow, M. E. Brokke, G. W. Moersch, M. E. Butler, C. F. Klein, W. A. Neuklis, and E. C. Y. Huang, *J. Org. Chem.*, **30**, 212 (1965).

(6) D. F. Morrow, M. E. Butler, and E. C. Y. Huang, *ibid.*, **30**, 579 (1965).

(7) G. Snatzke and A. Veithen, *Justus Liebigs Ann. Chem.*, **703**, 159 (1967).

(8) R. Zell, H. Brintzinger, B. Prijs, and H. Erlenmeyer, *Experientia*, **20**, 117 (1964).

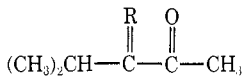
(9) H. E. Baumgarten and F. A. Bower, *J. Amer. Chem. Soc.*, **76**, 4561 (1954).

(10) W. H. Hartung, *ibid.*, **53**, 2248 (1931).

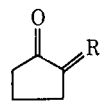
(11) O. Touster, *Org. React.*, **7**, 327 (1953).

In two cases, the α-amino ketones **7d** and **8d** were isolated.

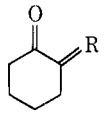
CHART I



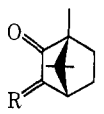
1a, R = H_2
b, R = *anti*-NOH
c, R = H and NH_3Cl



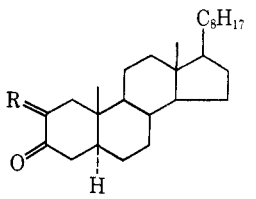
2a, R = H_2
b, R = NOH
c, R = H and NH_3Cl



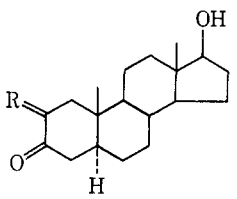
3a, R = H_2
b, R = NOH
c, R = H and NH_3Cl



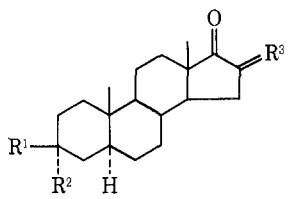
4a, R = H_2
b, R = *anti*-NOH
c, R = *exo*-H and *endo*-NH_3Cl



5a, R = H_2
b, R = *anti*-NOH

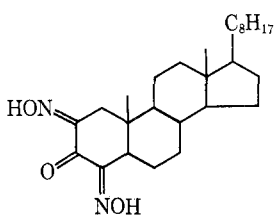


6a, R = H_2
b, R = *anti*-NOH
c, R = β-H and α-NH_3Cl



7a, R^1 = OH; R^2 = H; R^3 = H_2
b, R^1 = OH; R^2 = H; R^3 = *anti*-NOH
c, R^1 = OH; R^2 = H; R^3 = α-H and β-NH_3Cl
d, R^1 = OH; R^2 = H; R^3 = α-H and β-NH_2

8a, R^1 = H; R^2 = OH; R^3 = H_2
b, R^1 = H; R^2 = OH; R^3 = *anti*-NOH
c, R^1 = H; R^2 = OH; R^3 = α-H and β-NH_3Cl
d, R^1 = H; R^2 = OH; R^3 = α-H and β-NH_2



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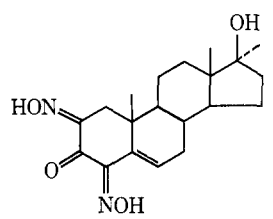

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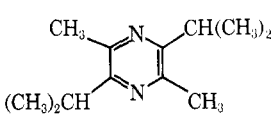

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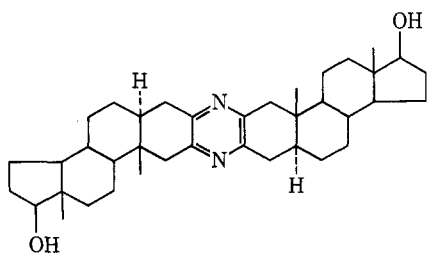

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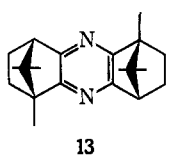

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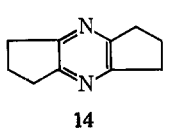

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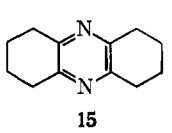

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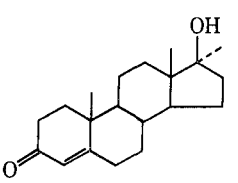
Results and Discussion

Synthesis of α-Oximino Ketones.—The successful nitrosation of several steroidal ketones,[12-14] including 5α-cholestan-3-one[12] (**5a**), 5α-androstan-17β-ol-3-one[13] (**6a**), and 5α-androstan-3β-ol-17-one[14] (**7a**) indicated that isoamyl nitrite or 2-octyl nitrite with potassium *tert*-butoxide in *tert*-butyl alcohol would be the most successful nitrosating agent. 2-Octyl nitrite was used to prepare 4-methyl-*anti*-3-oximino-2-pentanone[15] (**1b**), but the 2-oximino derivatives of cyclopentanone (**2a**) and cyclohexanone (**3a**) could not be prepared by nitrosation with 2-octyl nitrite in either a base-catalyzed or an acid-catalyzed reaction. Both 2-oximinocyclopentanone[16,17] (**2b**) and 2-oximinocyclohexanone[16,18] (**3b**) were prepared from the respective 2-ethoxycarbonyl cyclic ketones using sodium nitrite in sodium hydroxide.[17] As reported earlier,[18] **3b** was obtained only as a yellow oil. The latter was directly reduced to 2-aminocyclohexanone hydrochloride[19] (**3c**).

After (1*R*)-2-bornanone[20] (**4a**) [(+)-camphor] in *tert*-butyl alcohol was treated with 2-octyl nitrite in the presence of potassium *tert*-butoxide, none of the expected α-oximino ketone was isolated. Treatment of the sodium salt of **4a** in ether with 2-octyl nitrite gave (1*R*)-*anti*-3-oximino-2-bornanone[21] (**4b**).

The preparation of *anti*-2-oximino-5α-cholestan-3-one[12] (**5b**), *anti*-2-oximino-5α-androstan-17β-ol-3-one[13] (**6b**), *anti*-16-oximino-5α-androstan-3β-ol-17-one[14] (**7b**), and *anti*-16-oximino-5α-androstan-3α-ol-17-one (**8b**) was accomplished with a less than equivalent amount of 2-octyl nitrite in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol. Treatment of 17α-methyl-4-androsten-17β-ol-3-one (**16**) with a less than equivalent amount of 2-octyl nitrite led to a mixture of monooximino and bisoximino ketones from which no pure



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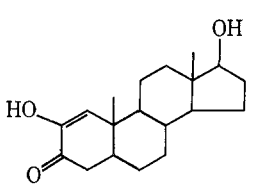
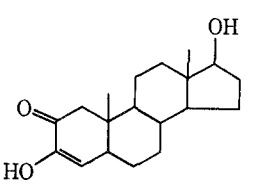


17a



17b

compound could be isolated. When a large excess of 2-octyl nitrite and potassium *tert*-butoxide is used with ketones with more than one site for nitrosation, the

(12) J. C. Sheehan and W. F. Erman, *J. Amer. Chem. Soc.*, **79**, 6050 (1957).
(13) G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.*, **13**, 1445 (1965); *Chem. Abstr.*, **64**, 9785c (1966).
(14) J. L. Mateos, O. Chao, and H. Flores R, *Tetrahedron*, **19**, 1051 (1963).
(15) K. L. Hoy and W. H. Hartung, *J. Org. Chem.*, **23**, 967 (1958).
(16) The configuration(s) of the carbon to nitrogen double bond(s) is (are) unassigned.
(17) A. C. Cope, L. L. Estes, Jr., J. R. Emery, and A. C. Haven, Jr., *J. Amer. Chem. Soc.*, **73**, 1199 (1951).
(18) T. A. Geissman and M. J. Schlatter, *J. Org. Chem.*, **11**, 771 (1946).
(19) H. E. Baumgarten and J. M. Petersen, *J. Amer. Chem. Soc.*, **82**, 459 (1960).
(20) A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, **1**, 371 (1947).
(21) L. Claisen and O. Manasse, *Justus Liebigs Ann. Chem.*, **274**, 71 (1893).

TABLE I

SPECTRAL DATA FOR SOME α-OXIMINO KETONES

	Absolute ethanol		1 N ethanolic KOH	
	Uv	CD	Uv	CD
Compd	λmax, nm (ε[a])	λmax, nm ([θ][b])	λmax, nm (ε[a])	λmax, nm ([θ][c])
1b	315 (43),[d] 231 (10,000)		380 (59), 282 (16,000)	
2b	243 (8700)[e]		*f*	
4b	335 (39), 242 (9300)	335 (+1400), 243 (+24,000)	380 (70),[d] 290 (15,000)	385 (+1000), 336 (−5300), 290 (+36,000)
5b	*g*	*g*	400 (77), 299 (14,000)	420 (+330), 334 (−1400), 300 (+1500)
6b	340 (33),[d] 243 (7300)	342 (+2600), 277 (−2000)	410 (62), 300 (13,000)	425 (+1200), 332 (−4700), 305 (+4500)
7b	344 (58), 239 (10,000)	347 (+5300), 263 (−8400)	385 (93),[d] 292 (17,000)	420 (−560), 322 (+7600), 287 (−6400)
8b	345 (52), 238 (9900)	347 (+5800), 263 (−8600)	385 (73),[d] 290 (22,000)	420 (−410), 387 (−380), 365 (−460), 323 (+5500), 285 (−8400)

[a] Molar absorptivity. [b] Molecular ellipticity at 25–28° with *c* 0.0020–0.085 g/100 ml. [c] Molecular ellipticity at 25–28° with *c* 0.00078–0.14 g/100 ml. [d] Shoulder. [e] No absorption maximum or shoulder detected at a wavelength longer than 243 nm. [f] Decomposed in 1 *N* ethanolic KOH. [g] Too insoluble for measurement.

α,α′-bisoximino ketones are formed. In this way both 2,4-bisoximinocholestan-3-one[16,22,23] (**9**) and 2,4-bisoximino-17α-methyl-5-androsten-17β-ol-3-one[16] (**10**) were prepared, the latter from 17α-methyl-4-androsten-17β-ol-3-one (**16**).

Among the α-oximino ketones in Chart I, there are only four (**1b**, **5b**, **6b**, and **10**) whose parent ketones possess more than one distinct site for nitrosation.[11] The structure of **1b** is known[15] and is now confirmed by its nmr spectrum. For both **5b** and **6b**, the 2-oximino structure was assigned earlier.[12,13] The structure of **6b** is now verified by its conversion with sodium sulfite in acetic acid to androstan-17β-ol-2,3-dione[22,24,25] (**17**), which in deuteriochloroform is a mixture of the enol ketones **17a** and **17b**, the nmr spectrum showing, as expected,[26] two distinct vinylic proton signals. The structure of **10** is assigned in analogy to the nitrosation of 4-androsten-17β-ol-3-one with *n*-butyl nitrite and potassium *tert*-butoxide in *tert*-butyl alcohol which gives 2,4-bisoximino-5-androsten-17β-ol-3-one.[23]

For the α-oximino ketones **1b**, **4b**, and **6b**–**8b**, the anti configuration for the carbon–nitrogen double bond is assigned on the basis of their uv (isotropic absorption) spectra (Table I), a bathochromic shift of 50–60 nm for the absorption band near 240 nm occurring when the solvent is changed from ethanol to 1 *N* ethanolic potassium hydroxide. For the syn configuration a shift of this magnitude is not to be expected.[14,27,28] The low solubility of **5b** in ethanol is such that its uv spectrum in this solvent could not be measured. It is assigned the anti configuration on the basis of the similarity of its uv spectrum in 1 *N* ethanolic potassium hydroxide to that of **6b** in the same solvent. The configurations of the oximino groups in **2b**, which decomposes in 1 *N* ethanolic potassium hydroxide, in **3b**, which was obtained as an oil,[18] and in the α,α′-bisoximino ketones **9** and **10** are not assigned.[23]

Synthesis of α-Amino Ketone Hydrochlorides.—As reported earlier,[15] 4-methyl-*anti*-3-oximino-2-pentanone (**1b**) is smoothly reduced with hydrogen over 10% palladium on carbon in absolute ethanol containing 3 mol of hydrogen chloride per mole of ketone. The same reaction was used to prepare 2α-amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**), 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**), and 16β-amino-5α-androstan-3α-ol-17-one hydrochloride (**8c**) from the respective α-oximino ketones (**6b**–**8b**). The insolubility of *anti*-2-oximino-5α-cholestan-3-one (**5b**) in ethanolic hydrogen chloride precluded its reduction by this procedure. Application of this method to the reduction of (1*R*)-*anti*-3-oximino-2-bornanone (**4b**) gave (1*R*,3*S*)-3-amino-2-bornanone hydrochloride[21] (**4c**) in 7% yield, 54% of **4b** being recovered. A more complete conversion of **4b** to **4c** was accomplished by reduction of **4b** with zinc in aqueous sodium hydroxide and subsequent treatment of the resulting α-amino ketone with hydrogen chloride.[21]

No characterizable product was obtained from the catalytic reduction of 2-oximinocyclopentanone (**2b**) while the same procedure when applied to 2-oximinocyclohexanone (**3b**) gave 2-aminocyclohexanone hydrochloride[19] (**3c**) in only 7% yield. As described earlier,[19] both 2-aminocyclopentanone hydrochloride (**2c**) and **3c** were prepared in good yield by treatment of cyclopentylamine and cyclohexylamine, respectively, with *tert*-butyl hypochlorite.

With the exception of **2c**, the structures of the α-amino ketone hydrochlorides in Chart I follow from the

(22) There is no direct evidence concerning the configuration at C-5 in this compound.

(23) M. P. Cava, E. J. Glamkowski, and P. M. Weintraub, *J. Org. Chem.*, **31**, 2755 (1966).

(24) H. Dannenbery, D. D.-v. Dresler, and T. Köhler, *Chem. Ber.*, **93**, 1989 (1960).

(25) M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947).

(26) C. R. Noller, A. Melera, M. Gut, J. N. Shoolery, and L. F. Johnson, *Tetrahedron Lett.*, No. 15, 15 (1960).

(27) D. H. R. Barton and J. M. Beaton, *J. Amer. Chem. Soc.*, **83**, 4083 (1961).

(28) M. P. Cava and B. R. Vogt, *J. Org. Chem.*, **30**, 3775 (1965).

structures of the α-oximino ketones from which they were prepared by reduction with hydrogen. The structure of **2c** was assigned earlier.[19]

The configuration of (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**) follows from its nmr spectrum and the known absolute configuration of (1*R*)-2-bornanone (**4a**).[20] As has been shown with (1*R*,3*S*)-3-amino-2-bornanone,[29] the C-3 proton signal in the nmr spectrum of **4c** is a doublet with a coupling constant of 4.5 Hz as the result of the coupling of the C-3 proton with that at C-4. Application of the Karplus relationship[30] gives a value of approximately 40° for the dihedral angle between the C-3 and C-4 protons. Hence, the hydrogen atom at C-3 has the exo and the ammonium group has the endo configuration.

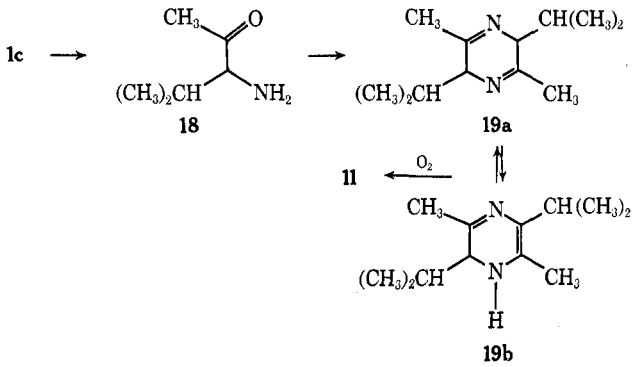
The configuration at C-2 in 2α-amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**) is assigned on the assumption that the reduction of **6b** in strong acidic medium gives the more thermodynamically stable, equatorial epimer. This assignment is confirmed by CD studies of the α-amino ketone hydrochlorides discussed below.

The configuration at C-16 for 16β-amino-5α-androstan-3β- and -3α-ol-17-one hydrochloride (**7c** and **8c**) is assigned in analogy to the assignments made for 16-bromo-17-keto steroids.[31,32] The 16α and 16β bonds in the latter are bisectional,[31,32] each possessing the same degree of axial and equatorial character.[32] A substituent at either the 16α or 16β position will then have the same dihedral angle with the carbonyl bond. Equilibration studies of 16α- and 16β-bromo-5α-androstan-17-one[33] show that the 16β-bromo isomer is the more thermodynamically stable. Dipole–dipole interactions of the C-16 substituents with the carbonyl group must play only a minor role in this difference in stability. It is a good assumption that for the 16α- and 16β-amino hydrochloride derivatives of 17-keto steroids, it is the 16β-ammonium epimer which is the more thermodynamically stable. Also since the angular methyl group at C-13 shields the β face of a 16-oximino 17-keto steroid,[34] the kinetically controlled product of the catalytic reduction is the 16β-ammonium isomer.

Dimerization of α-Amino Ketones.—Treatment of 3-amino-4-methyl-2-pentanone hydrochloride[15] (**1c**) with 10% aqueous sodium hydroxide resulted in the dimerization of the resulting α-amino ketone **18** to a mixture of the dihydropyrazines **19** (Scheme I). This mixture is spontaneously oxidized by air to 2,5-diisopropyl-3,6-dimethylpyrazine (**11**). An ethereal extract of the reaction mixture was examined immediately, and its nmr spectrum showed signals only for the α-amino ketone **18** and the pyrazine **11**. When an aqueous solution of this material containing sodium hydroxide stood at room temperature, **11** precipitated. No dihydropyrazine was detected. Without direct evidence, it is assumed that the mixture of dihydropyrazines is composed of a number of substances, **19a**, **19b**, and other double bond isomers of **19a** and **19b**.

(29) O. E. Edwards and M. Lesage, *Can. J. Chem.*, **41**, 1592 (1963).
(30) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(31) J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960).
(32) F. V. Brutcher, Jr., and W. Bauer, Jr., *J. Amer. Chem. Soc.*, **84**, 2236 (1962).
(33) J. Fajkos, *J. Chem. Soc.*, 3966 (1959).
(34) J. Fishman, *J. Org. Chem.*, **31**, 520 (1966).

SCHEME I

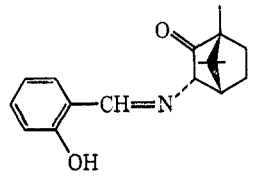


An aqueous solution of 2α-amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**) was neutralized with aqueous sodium carbonate. The resulting yellow precipitate had an ir spectrum which showed weak carbonyl absorption at 1730 cm^{-1} and a stronger, broad band near 1670 cm^{-1}. The latter is attributed to the azomethine group of the dihydropyrazines. When the precipitate was dissolved in ethanol containing a trace of *p*-toluenesulfonic acid, the solution immediately became dark orange, and during 30 min di-(17β-hydroxy-5α-androstano)[2,3-*b*:2′,3′-*e*]pyrazine (**12**) precipitated as white needles.

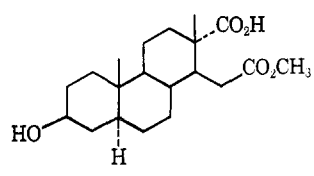
An aqueous solution of (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**) was neutralized with 10% aqueous sodium hydroxide. A carbon tetrachloride extract of the reaction mixture was examined immediately. Its nmr spectrum showed signals for only the α-amino ketone. In subsequent spectra, these signals decreased in intensity and in 11.5 hr were replaced by other signals. The latter are assigned to a mixture of the dihydropyrazines. Preparative tlc on silica gel separated this mixture into three fractions. Removal of the main fraction and its reexamination with tlc separated the material into the same three fractions.

The pyrazine **13** was not detected in any of these experiments. Also, the α-amino ketone could not be isolated free of the dihydropyrazines. Treatment of an ethereal solution of the α-amino ketone with salicylaldehyde gave (1*R*,3*S*)-3-salicylidenimino-2-bornanone (**20**).

A methanolic solution of 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**) was neutralized with 10% aqueous sodium hydroxide. The solution was stirred in air overnight. After dilution with water, no product was extracted from this solution with ether. Upon acidification of the solution, the 16-methyl ester of 16,17-*seco*-5α-androstan-3β-ol-16,17-dioic acid (**21**) was isolated.



20

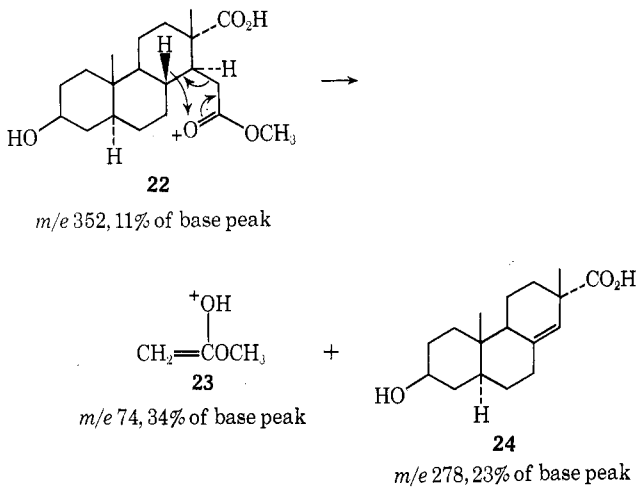


21

The ir and nmr spectra and other properties of this acid were compatible with **21** but also with the 17-methyl ester as an alternate. The mass spectrum of the compound has a parent ion (**22**) with *m/e* 352 and

two other significant ions with *m/e* 74 and 278. That with *m/e* 74 corresponds to a fragment (**23**) from a methyl ester possessing a γ-hydrogen atom capable of cleavage while undergoing a McLafferty rearrangement[35] (Scheme II). The ion with *m/e* 278 corresponds

SCHEME II



to the residual molecular fragment **24** after rearrangement. The 17-methyl ester molecular ion when rearranged would result in an ion of the same mass.

In another experiment, an aqueous solution of 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**) was neutralized with aqueous sodium bicarbonate. A yellow precipitate of 16β-amino-5α-androstan-3β-ol-17-one (**7d**) formed. Although it was stable as the amorphous solid and as a solution in methanol under nitrogen, it could not be crystallized. Identification was made on the basis of its ir and mass spectra, but it was not characterized further. Heating of a benzene or of a chloroform solution of **7d** containing a trace of *p*-toluenesulfonic acid and then removal of the solvent gave an oil which on examination of its ir spectrum showed reduced carbonyl absorption at 1750 cm^{-1} and a very broad absorption at 1670–1730 cm^{-1}. The spectrum indicated that condensation to the dihydropyrazines had occurred. No pure compound could be isolated from this mixture.

Similarly, an aqueous solution of 16β-amino-5α-androstan-3α-ol-17-one hydrochloride (**8c**) was neutralized with aqueous sodium bicarbonate. The corresponding 16β-amino-5α-androstan-3α-ol-17-one (**8d**) was isolated. This α-amino ketone was also stable as the crystalline, yellow solid or as a methanolic solution under nitrogen. It was reprecipitated from ether on cooling. The original α-amino ketone hydrochloride **8c** and 16β-salicylidenimino-5α-androstan-3α-ol-17-one were readily prepared from the free base. The α-amino ketone apparently forms a mixture of dihydropyrazines when heated in chloroform containing a trace of *p*-toluenesulfonic acid. No pure compound could be isolated from this mixture.

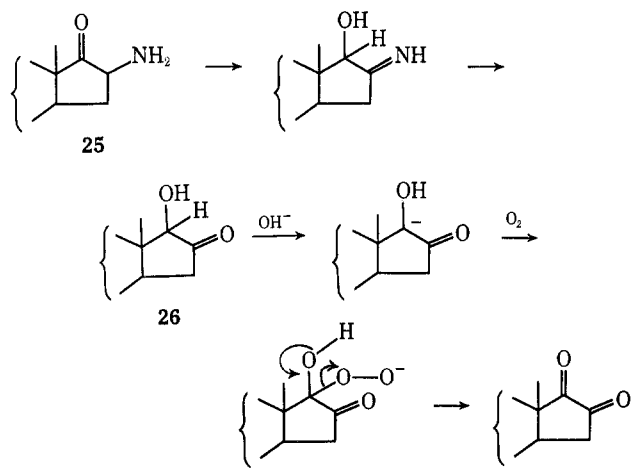
Oxidation of Dihydropyrazines.—A mixture of dihydropyrazines with alkyl or with cyclohexano substituents are spontaneously oxidized in air.[8,9] (1*R*,3*S*)-3-Amino-2-bornanone and the 16β-amino-5α-androstan-17-ones form dihydropyrazines which are stable in air. The reported[9] rapid oxidation with hydrogen peroxide in potassium hydroxide of the dihydropyrazines from dimerization of 2-aminocyclohexanone suggested the use of this reagent for the oxidation of the air stable dihydropyrazines.

Using this reagent, an attempt was made to oxidize the dihydropyrazine mixture formed from 16β-amino-5α-androstan-3α-ol-17-one hydrochloride (**8c**). No basic or neutral material was isolated from this reaction. The product was an acid which, although not completely characterized, is assumed to be the *seco*-16,17-dioic acid. This conclusion is based on the similarity of this peroxide oxidation to the air oxidation of 16β-amino-5α-androstan-3β-ol-17-one in methanolic sodium hydroxide and on the examination of the products formed on treatment of 2-aminocyclopentanone hydrochloride[19] (**2c**) and 2-aminocyclohexanone hydrochloride[9,19] (**3c**) with aqueous potassium hydroxide and then hydrogen peroxide.

With these reagents, **2c** gave dicyclopentano[*b*,*e*]pyrazine (**14**) in 47% yield. After acidification of the reaction mixture there was also obtained a small amount of glutaric acid. Also, **3c** was converted to dicyclohexano[*b*,*e*]pyrazine[9,36,37] (**15**) and adipic acid in 35 and 38% yield, respectively. No reference to adipic acid was made in the original report of the latter oxidation.[9]

A route for the formation of the *seco*-16,17-dioic acid from 16β-amino-5α-androstan-3α-ol-17-one (**8d**) as well as glutaric and adipic acid is shown in Scheme III.

SCHEME III



This same route will explain the formation of the 16-methyl ester of 16,17-*seco*-5α-androstan-3β-ol-16,17-dioic acid (**21**) on treatment of 16β-amino-5α-androstan-3β-ol-17-one hydrochloride (**7c**) in methanol with sodium hydroxide. As seen in Scheme III, an α-amino ketone **25** is converted to the α-hydroxy ketone **26**. A similar acid-catalyzed conversion was proposed to explain the conversion of 16ξ-amino-5-androsten-3β-ol-17-one to 5-androsten-3β,17β-diol-16-one.[4] A steroidal 2,3-dione was found to be oxidized to a *seco*-2,3-dioic acid with an aqueous mixture of potassium hydroxide and hydrogen peroxide.[38]

(35) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 155–162 and 176–178.

(36) An alternate name for **15** is 1,2,3,4,6,7,8,9-octahydrophenazine.

(37) P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 323 (1948).

(38) R. Hanna and G. Ourisson, *Bull. Soc. Chim. Fr.*, 1945 (1961).

After the mixture of dihydropyrazines formed from (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**) was heated with an aqueous mixture of potassium hydroxide and hydrogen peroxide, the mixture of dihydropyrazines was recovered unchanged. The mixture is readily oxidized in dioxane–water with sulfuric acid–sodium nitrite,[39] and di[(1*R*)-bornano][2,3-*b*:2′,3′-*e*]pyrazine[39] (**13**) was isolated.

Circular Dichroism Studies.—For the α-oximino ketones in absolute ethanol the weak uv absorption maximum at 315–345 nm (Table I) is assigned to the n → π* transition of the carbonyl group. Assuming that the α-oximino carbonyl chromophore is rotationally similar to a cisoid α,β-unsaturated ketone and that the preferred chirality of the chromophore fixes the sign of the Cotton effect associated with the carbonyl n → π* transition,[40,41] the observed positive Cotton effect (Table I) is predicted for this transition of *anti*-2-oximino-5α-androstan-17β-ol-3-one (**6b**).[42] In an octant projection,[41] the oximino π bond lies in the lower right or upper left far octant. The sign of this Cotton effect is the same but the molecular ellipticity at the maximum is about one-half that of the carbonyl n → π* transition Cotton effect of the parent ketone **6a** (Table II). Similarly, the observed positive Cotton effect is predicted for *anti*-16-oximino-5α-androstan-3β- and -3α-ol-17-one (**7b** and **8b**). Again, this Cotton effect is of the same sign but reduced in molecular ellipticity as compared with the carbonyl n → π* Cotton effect in the parent ketones. In **7b** and **8b**, the CD maxima are similar in sign and magnitude to that at 354 nm ([θ] +5700) shown by 16-methylene-19-norandrost-4-en-17-one[43] (**27**). In the octant projections of **7b**, **8b**, and **27**, the carbon–nitrogen or the carbon–carbon π bond at C-16 lies in the lower right or upper left far octant.

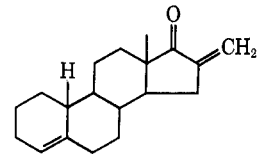
TABLE II

SPECTRAL DATA FOR SOME α-AMINO KETONE HYDROCHLORIDES IN ABSOLUTE ETHANOL

Compd	Uv λ_{max}, nm (ϵ^a)	CD λ_{max}, nm ($[\theta]^b$)
4a	290 (31)	295 (+5300)
4c	295 (27)[c]	318 (+1800),[c,d] 310 (+2200), 275 (−480)
6a	285 (22)	288 (+4400)
6c	284 (27)	286 (+5800)
7a	300 (40)	297 (+13,000)[e]
7c	300 (32)	309 (+8000)
8a	295 (43)	297 (+13,000)
8c	300 (36)	309 (+8100)

[a] Molar absorptivity. [b] Molecular ellipticity at 25–28° with *c* 0.010–0.10 g/100 ml. [c] Methanol was the solvent for this spectrum. [d] Shoulder.

In the CD spectra of **6b**, **7b**, and **8b** in absolute ethanol, there is also a negative maximum near 270 nm. This maximum is tentatively assigned to the nitrogen n → π* transition. The isotropic absorption band associated with this CD maximum is obscured by the strong π → π* absorption band centered near 240 nm. The latter absorption band is very intense and any CD associated with the transition could not be observed.



27

The oximino group and the carbonyl group in (1*R*)-*anti*-3-oximino-2-bornanone (**4b**) are coplanar. A positive CD maximum at 335 nm is observed for the carbonyl n → π* transition of **4b** in absolute ethanol. No dichroic absorption maximum in the 263–277-nm region was observed, but a strong positive maximum at 243 nm is associated with the π → π* transition. The absence of an oximino n → π* and the observation of a strong π → π* dichroic absorption band in the spectrum of **4b** is similar to observations made with optically active saturated oximes and testosterone oxime.[42] For these compounds only Cotton effects associated with a π → π* transition are observed.

When the α-oximino ketones are dissolved in 1 *N* ethanolic potassium hydroxide, the anionic form of the chromophore is produced. The uv bands due to the carbonyl n → π* and π → π* transitions are now at 380–410 and 280–300 nm, respectively. These transitions give rise to CD maxima. A CD maximum, tentatively assigned to the n → π* transition of the oximino group is also found near 330 nm. The uv absorption band for this latter transition is obscured by the π → π* absorption band at 280–300 nm. For **4b** and **6b** in 1 *N* ethanolic potassium hydroxide, the signs of the respective Cotton effects are the same as those in ethanol. There is probably a small distortion in the preferred conformations of the respective rings and now a negative CD maximum is observed for the oximino n → π* transition in **4b**. For **7b** and **8b**, the respective CD maxima have changed sign. This probably reflects a large change in the preferred conformation of the D ring.

As seen in Table II, introduction of an ammonium chloride group α to a carbonyl group has little effect on the carbonyl n → π* isotropic absorption maximum near 295 nm.

As has been noted with lycopodium alkaloids,[44] a positive charge on nitrogen makes an antioctant contribution[45] to the ORD. The negative Cotton effect displayed by 17aβ-methyl-17aα-methylamino-D-homoandrost-5-en-3β-ol-17-one hydrochloride and 17aα-amino-17aβ-methyl-D-homoandrost-5-en-3β-ol-17-one hydrochloride near 300 nm has also been explained on this basis.[5] Also in β-amino adamantanones, a positive charge on nitrogen has been reported to give an antioctant contribution.[46] This conclusion is confirmed

(39) R. C. Cookson, J. Hudec, A. Szabo, and G. E. Usher, *Tetrahedron*, **24**, 4353 (1968).

(40) G. Snatzke, *Tetrahedron*, **21**, 413 (1965).

(41) G. Snatzke, *ibid.*, **21**, 439 (1965).

(42) A number of exceptions to this rule have been noted by P. Crabbé and L. Pinelo, *Chem. Ind. (London)*, 158 (1966).

(43) P. Crabbé, "Optical Rotary Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 216.

(44) W. A. Ayer, J. A. Berezowsky, and D. A. Law, *Can. J. Chem.*, **41**, 649 (1963).

(45) If in an octant projection,[40] a group lying in an upper left or lower right far octant makes a negative contribution to the magnitude of the Cotton effect associated with the carbonyl n → π* transition, it is said to make an antioctant contribution to the ORD and CD or to display antioctant behavior.

(46) G. Snatzke and G. Eckhardt, *Tetrahedron*, **26**, 1143 (1970).

using the data in Table II. For (1*R*,3*S*)-3-amino-2-bornanone hydrochloride (**4c**), the ammonium group lies in an upper left or lower right far octant and the molecular ellipticity for the positive CD maximum, as compared to that of **4a** (Table II), is reduced. For **6c** the equatorial ammonium group causes a slight increase in the molecular ellipticity of the positive CD maximum near 287 nm. As expected with a 16β-ammonium group in **7c** and **8c**, the molecular ellipticity of the respective positive CD maxima is reduced.

The uv spectra of the pyrazines **11**, **14**, and **15** in methanol and in sulfuric acid were summarized and discussed in a preliminary report.[2] The uv and CD spectra of **12** in chloroform and **13** in methanol and in sulfuric acid were also shown and analyzed.[2] Details of these measurements as well as the ORD data for **12** and **13** are given in the Experimental Section.

Biological Activity.—The steroidal α-oximino ketones **5b**, **6b**, **7b**, **9**, and **10** were screened for general endocrine activity in rats.[47,48] All show essentially no activity. *anti*-16-Oximino-5α-androstan-3α-ol-17-one (**8b**) and the α-amino ketone hydrochlorides **7c** and **8c** were tested for androgenic activity.[48] In these tests, **8b** has a low androgenic activity but less than 5% of that of testosterone, whereas **7c** and **8c** are inactive. 2α-Amino-5α-androstan-17β-ol-3-one hydrochloride (**6c**) has no androgenic activity but shows moderate anti-uterotropic activity[49] at a high dose against estrone. It, however, is toxic as three of eight mice died in the test with the stimulator and five of eight mice died when **6c** was tested at a high dose by itself.

Experimental Section

Melting points were taken in capillary tubes and are corrected. Boiling points are not corrected. Optical rotations at the sodium D line were measured using a visual polarimeter and 1-dm sample tubes. Infrared absorption (ir) spectra were obtained with a Beckman Model IR-10 spectrophotometer.

Nuclear magnetic resonance (nmr) spectra were observed with a Varian Model A-60 spectrometer operating at 60 MHz. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane except when deuterium oxide (D_2O) was the solvent. As is indicated with these spectra, the chemical shifts are referenced to an internal standard of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS). Coupling constants (J) are estimated to ± 0.5 Hz. In reporting the nmr spectra the following abbreviations are used: singlet, s; broad singlet, bs; doublet, d; triplet, t; septet, sept; multiplet, m.

Isotropic ultraviolet absorption (uv) spectra were obtained with a Cary Model 14 spectrophotometer using matched 1-cm cells and the normal variable slit.

Circular dichroism (CD) spectra and optical rotatory dispersion (ORD) curves were measured using a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory. The slit was programmed for a spectral band width of 1.5 nm, and a 1-cm cell was used. Cut-off was indicated when the dynode voltage reached 400 V for CD and 800 V for ORD measurements. In reporting these spectra the following abbreviations are used: maximum, max; minimum, min; peak, pk; trough, tr; inflection, infl; shoulder, sh; cut-off, c-off.

Mass spectra were obtained using a LKB Type 9000 mass spectrometer. The ionizing voltage was 70 eV. Only pertinent m/e values are reported. A molecular ion is indicated as M^+.

Elemental analyses and osmometric molecular weight determinations were done by Galbraith Laboratories, Knoxville, Tenn. The elemental composition of an α-oximino ketone is somewhat difficult to determine by combustion analysis. The general trend is for the percentage of nitrogen to be estimated correctly after combustion at the usual temperature. The estimated percentage of carbon, however, is consistently low and the estimated percentage of hydrogen is frequently incorrect. To overcome this difficulty, it is necessary to raise the combustion temperature higher than that normally used.

The purity of the compounds reported was verified by tlc which, in all cases, except as is discussed for **17**, indicated the presence of only one compound.

4-Methyl-*anti*-3-oximino-2-pentanone (**1b**) was prepared from 4-methyl-2-pentanone (**1a**) by an adaptation of an acid-catalyzed nitrosation technique[15] using 2-octyl nitrite.[50] Two recrystallizations of the crude product (78%) from petroleum ether (bp 40–60°) gave **1b** (29%) as long, white prisms: mp 76–78° (lit.[15] mp 76–77°); ir (KBr) 1670 (broad, C=N and C=O) and 3220 cm^{-1} (OH); nmr (CCl_4) δ 1.21 (d, 6, J = 7.0 Hz, C-4 CH_3 and C-5 H), 2.31 (s, 3, C-1 H), 3.36 (sept, 1, J = 7.0 Hz, C-4 H), and 9.05 ppm (bs, 1, OH).

3-Amino-4-methyl-2-pentanone Hydrochloride (**1c**).—At room temperature and atmospheric pressure, 1.47 g (11.4 mmol) of **1b** in 85 ml of absolute ethanol containing 1.29 g (35.4 mmol) of hydrogen chloride was reduced with hydrogen over 0.124 g of 10% palladium on carbon. After reduction, the catalyst was removed by filtration, and most of the solvent was evaporated at reduced pressure. Addition of ether caused the precipitation of crude **1c** (90%). Recrystallization from absolute ethanol–ether gave **1c** (51%) as fine, white prisms: mp 156–157° dec (lit. melting point one degree range between 150 and 160° with dec[15] and 153.5–154°[51]); ir (KBr) 1595 ($^+NH_3$) and 1730 cm^{-1} (C=O); nmr (D_2O–DSS) δ 0.90 (d, 3, J = 7.0 Hz, C-4 CH_3 or C-5 H), 1.14 (d, 3, J = 7.0 Hz, C-4 CH_3 or C-5 H), 2.35 (s, 3, C-1 H), 2.63 (m, 1, J = 4.0 and 7.0 Hz, C-4 H), 4.28 (d, 1, J = 4.0 Hz, C-3 H), and 6.29 ppm (s, 3, $^+NH_3$ exchanging).

2-Oximinocyclopentanone (**2b**).—2-Ethoxycarbonylcyclopentanone,[52] bp 100–104° (12 mm), was nitrosated with sodium nitrite in aqueous sodium hydroxide.[17] Recrystallization of the crude product (46%) from ether–petroleum ether (bp 40–60°) gave **2b** (21%): mp 68–70° [lit.[17] mp 65.5–67° (monohydrate) and 78.5–81° (hemihydrate)]; ir (KBr) 1645 (C=N), 1700 (C=O), 3580 cm^{-1} (OH).

2-Aminocyclopentanone Hydrochloride (**2c**).—Cyclopentanone was oxidized[19] with freshly distilled *tert*-butyl hypochlorite.[53] The crude product, a black tar, was triturated twice with isopropyl alcohol containing 1 ml of concentrated hydrochloric acid per 100 ml of alcohol. The combined alcoholic solutions were decolorized with Norite, diluted with an equal volume of ether, and refrigerated for 12 hr during which crude **2c** precipitated. Three recrystallizations of this solid from methanol–water gave **2c** (15%) as clusters of fine, white prisms: mp 142–144° dec (lit.[19] mp 146–147° dec); ir (KBr) 1615 ($^+NH_3$) and 1760 cm^{-1} (C=O); nmr (D_2O–DSS) δ 2.28 (m, 6, C-3 H, C-4 H, and C-5 H), 4.00 (m, 1, C-2 H), and 4.61 ppm (s, 3, $^+NH_3$ exchanging).

Anal. Calcd for $C_5H_{10}ClNO$: C, 44.29; H, 7.43; Cl, 26.15; N, 10.33; mol wt, 135.60. Found: C, 44.08; H, 8.00; Cl, 25.75; N, 10.18; mol wt (mass spectrum), 99 (M^+ − HCl = 99.13).

2-Oximinocyclohexanone (**3b**).—2-Ethoxycarbonylcyclohexanone was nitrosated with sodium nitrite in aqueous sodium hydroxide.[17] The resulting acidic aqueous solution of **3b** was extracted thoroughly with ether. The combined ether extracts were dried ($MgSO_4$) and the ether was evaporated at reduced pressure. Crude **3b** (56%) was thus obtained as a yellow oil (lit.[18] yellow oil).

2-Aminocyclohexanone Hydrochloride (**3c**).—As described for the preparation of **1c**, 9.11 g (71.7 mmol) of crude **3b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. The 5.00 g (47%) of crude **3c** was re-

(47) All screenings for biological activity were provided for by the Endocrine Evaluation Branch, General Laboratories and Clinics, National Cancer Institute, National Institutes of Health, Bethesda, Md.

(48) A. G. Hilgar and D. J. Hummel, Ed., "Androgenic and Myogenic Endocrine Bioassay Data," Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Bethesda, Md., Aug 1964.

(49) A. G. Hilgar and L. C. Trench, Ed., "Uterotropic Endocrine Bioassay Data," General Laboratories and Clinics, National Cancer Institute, National Institutes of Health, Bethesda, Md., June 1968.

(50) Prepared by the method of M. Pezold and R. L. Shriner, *J. Amer. Chem. Soc.*, **54**, 4707 (1932), and had bp 71–75° (35 mm).

(51) F. E. Lehmann, A. Bretscher, H. Kühne, E. Sorkin, M. Erne, and H. Erlenmeyer, *Helv. Chim. Acta*, **33**, 1217 (1950).

(52) P. S. Pinkney, *Org. Syn.*, **17**, 30 (1937).

(53) Prepared by the method of H. M. Teeter and E. W. Bell, *ibid.*, **32**, 20 (1952), and had bp 78–79°.

crystallized twice from isopropyl alcohol–ether (Norit) followed by three recrystallizations from *n*-propyl alcohol–ether. Thus was obtained 0.764 g (7%) of **3c** as very fine, white prisms: mp 150–151° dec (lit.[19] mp 156° dec); ir (KBr) 1590 ($^+NH_3$) and 1730 cm^{-1} (C=O); nmr (D_2O–DSS) δ 1.85 (m, 6, C-3, C-4, and C-5 H), 2.52 (m, 2, C-6 H), 4.15 (m, 1, C-2 H), and 4.62 ppm (s, 3, $^+NH_3$ exchanging).

Cyclohexylamine was oxidized[19] with freshly distilled *tert*-butyl hypochlorite.[53] The crude product (55%) was recrystallized twice from isopropyl alcohol–ether (Norit). Thus was obtained **3c** (20%): mp 153–155° dec; ir identical with that of **3c** prepared by the reduction of 2-oximinocyclohexanone (**3b**).

(1*R*)-*anti*-3-Oximino-2-bornanone (**4b**).—As described previously,[21] (1*R*)-2-bornanone (**4a**), mp 173–175°, $[\alpha]^{25}D$ +46° (*c* 1.00, absolute C_2H_5OH) [lit. mp 176.3–176.5°,[54] $[\alpha]^{25}D$ +41.4 (*c* 0.7643, alcohol)[55]], was converted in ether to its sodium salt, and the latter was nitrosated with 2-octyl nitrite.[50] Pure **4b** (16%) was white prisms and had mp 150–154°; $[\alpha]^{24}D$ +198° (*c* 1.00, absolute C_2H_5OH) [lit. mp 153–154°;[21] $[\alpha]D$ +197.0° ($CHCl_3$)[56]]; ir (KBr) 1645 (C=N), 1745 (C=O), and 3400 cm^{-1} (broad, OH); nmr (CCl_4) δ 0.89 and 1.00 (two s, 3 and 6, respectively, C-8, C-9, and C-10 H), 1.67 (m, 4, C-5 and C-6 H), and 3.25 ppm (m, 1, C-4 H).

(1*R*,3*S*)-3-Amino-2-bornanone Hydrochloride (**4c**).—As described for the reduction of **1b** to **1c**, **4b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. Recrystallization of the crude product from methanol–ether and then sublimation at 135° (2 mm) gave **4c** (7%): mp 207–212° dec; $[\alpha]^{24}D$ +26° (*c* 1.01, absolute C_2H_5OH) (lit. mp 223–225° dec[21] and 223–225°[57]).

The mother liquors from the recrystallization of **4c** were evaporated. Recrystallization of the residue from petroleum ether (bp 40–60°) gave crude **4b** (54%). Recrystallization from petroleum ether–ether (Norit) gave **4b** (38%), mp 152–154°.

Using the previously described procedure,[21] 3.17 g (17.5 mmol) of **4b** was reduced with zinc in aqueous sodium hydroxide. After the reduction was complete, the reaction mixture was thoroughly extracted with ether. The ethereal solution was dried (K_2CO_3), filtered, and then saturated with hydrogen chloride. Refrigeration of the solution for 12 hr resulted in the precipitation of 2.62 g (74%) of **4c** as white, microscopic prisms: mp 241–242° dec; $[\alpha]^{25}D$ +21° (*c* 1.28, CH_3OH); ir (KBr) 1600 ($^+NH_3$) and 1760 cm^{-1} (C=O); nmr (C_2D_5OD) δ 0.98 and 1.13 (two s, 6 and 3, respectively, C-8, C-9, and C-10 H), 1.82 (m, 4, C-5 and C-6 H), 2.62 (m, 1, C-4 H), 4.03 (d, 1, J = 4.5 Hz, C-3 H), and 5.57 ppm (s, 3, $^+NH_3$ exchanging).

***anti*-2-Oximino-5α-cholestan-3-one** (**5b**).—Under nitrogen, 0.421 g (0.0108 g-atom) of potassium was dissolved in 25 ml of dry *tert*-butyl alcohol. To this solution was added 0.752 g (1.94 mmol) of 5α-cholestan-3-one (**5a**), mp 129–131°, $[\alpha]^{26}D$ +40° (*c* 1.03, $CHCl_3$) [lit.[58] mp 129°, $[\alpha]D$ +41° ($CHCl_3$)], and then, by dropwise addition with stirring, 0.202 g (1.27 mmol) of 2-octyl nitrite[50] in 10 ml of dry *tert*-butyl alcohol. Stirring was continued for 2 hr. The reaction mixture was poured into 1 l. of ice water which was then acidified with dilute hydrochloric acid. The slightly acidic solution was refrigerated for 24 hr and the precipitate was collected by filtration. The solid was washed with water. Trituration with two 50-ml portions of acetone left 0.284 g (54%) of **5b** as white, microscopic cubes: mp 256–258° dec (lit.[12] mp 203–205°); $[\alpha]^{26}D$ +95° (*c* 1.00, 1 *N* ethanolic KOH); ir (KBr) 1620 (C=N), 1720 (C=O), and 3150 cm^{-1} (OH).

***anti*-2-Oximino-5α-androstan-17β-ol-3-one** (**6b**).—As described for the preparation of **5b**, 5α-androstan-17β-ol-3-one (**6a**), mp 170–175°, $[\alpha]^{26}D$ +33° (*c* 1.02, absolute C_2H_5OH) [lit.[59] mp 181°, $[\alpha]D$ +32° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide using 2-octyl nitrite.[50] After dilution of the reaction mixture with water and acidification, the crude reaction product was too gelatinous for the usual isolation by filtration. Instead, the material was extracted into ether. The ethereal solvent was evaporated, and the residue thoroughly washed with water. After two recrystallizations from methanol, **6b** (12%) was white, microscopic plates: mp 265–268° dec; $[\alpha]^{26}D$ +67° (*c* 0.243, absolute C_2H_5OH) [lit.[13] mp 266–267°; $[\alpha]D$ +48.1° (*c* 0.77, pyridine)]; ir (KBr) 1620 (C=N), 1720 (C=O), 3150 (very broad, OH), 3480 (broad, OH), and 3620 cm^{-1} (OH).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.08; H, 9.45; N, 4.17.

2α-Amino-5α-androstan-17β-ol-3-one Hydrochloride (**6c**).—As described for the reduction of **1b** to **1c**, **6b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. The crude hydrochloride (36%), mp >300° dec, was recrystallized from isopropyl alcohol–ether (Norit). Recrystallization then from methanol–ether gave **6c** (14%) as white, microscopic prisms: mp >300° dec; $[\alpha]^{25}D$ +40° (*c* 1.12, absolute C_2H_5OH); ir (KBr) 1720 (C=O), 3245 (broad, OH), and 3450 cm^{-1} (OH); nmr (CD_3OD) δ 0.77 (s, 3, C-18 or C-19 H), 1.20 (s, 3, C-18 or C-19 H), 4.18 (m, 1, C-2 H), and 4.78 ppm (s, 4, $^+NH_3$, and OH exchanging).

Anal. Calcd for $C_{19}H_{32}ClNO_2$: C, 66.75; H, 9.43; Cl, 10.37; N, 4.10. Found: C, 66.84; H, 9.50; Cl, 10.47; N, 4.09.

***anti*-16-Oximino-5α-androstan-3β-ol-17-one** (**7b**).—As described for the preparation of **5b**, 5α-androstan-3β-ol-17-one (**7a**), mp 173–175°, $[\alpha]^{25}D$ +90° (*c* 1.00, absolute C_2H_5OH) [lit.[59] mp 175°, $[\alpha]D$ +88° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide using 2-octyl nitrite.[50] Recrystallization of the crude product from methanol gave **7b** (43%) as white needles: mp 236–241° dec (lit. mp 245–247°[14] and 218–219.5°[60] dec); $[\alpha]^{26}D$ −15° (*c* 1.00, absolute C_2H_5OH); ir (KBr) 1635 (C=N) and 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.45; H, 9.17; N, 4.32.

16β-Amino-5α-androstan-3β-ol-17-one Hydrochloride (**7c**).—As described for the reduction of **1b** to **1c**, **7b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. Recrystallization of the crude hydrochloride from ethanol–ether gave **7c** (41%) as white, microscopic prisms: mp >300° dec; $[\alpha]^{26}D$ +74° (*c* 1.06, absolute C_2H_5OH); ir (KBr) 1615 ($^+NH_3$), 1765 (C=O), and 3310 cm^{-1} (OH); nmr (CD_3OD) δ 0.89 (s, 3, C-18 or C-19 H), 0.98 (s, 3, C-18 or C-19 H), and 4.80 ppm (s, 4, $^+NH_3$ and OH exchanging).

Anal. Calcd for $C_{19}H_{32}ClNO_2$: C, 66.75; H, 9.43; Cl, 10.37; N, 4.10. Found: C, 66.50; H, 9.33; Cl, 10.44; N, 4.29.

***anti*-16-Oximino-5α-androstan-3α-ol-17-one** (**8b**).—As described for the preparation of **5b**, 5α-androstan-3α-ol-17-one (**8a**), mp 182–185°, $[\alpha]^{26}D$ +95° (*c* 1.03, absolute C_2H_5OH) [lit.[59] mp 183°, $[\alpha]D$ +94.5° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide with 2-octyl nitrite.[50] Recrystallization of the crude product (100%) from methanol gave **8b** (70%) as white platelets: mp 217–219° dec; $[\alpha]^{27}D$ −20° (*c* 1.00, absolute C_2H_5OH); ir (KBr) 1635 (C=N), 1750 (C=O), 3150 (broad, OH), and 3520 cm^{-1} (sharp, OH).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.40; H, 9.13; N, 4.42.

16β-Amino-5α-androstan-3α-ol-17-one Hydrochloride (**8c**).—As described for the reduction of **1b** to **1c**, **8b** in ethanolic hydrogen chloride was reduced with hydrogen over 10% palladium on carbon. Recrystallization of the crude hydrochloride (84%) from absolute ethanol gave pure **8c** (32%) as very fine, white prisms: mp 255–259° dec; $[\alpha]^{26}D$ +81° (*c* 0.751, absolute C_2H_5OH); ir (KBr) 1640 ($^+NH_3$), 1765 (C=O), and 3360 cm^{-1} (OH); nmr (CD_3OD) δ 0.90 (s, 3, C-18 or C-19 H), 1.01 (s, 3, C-18 or C-19 H), and 4.80 ppm (s, 4, $^+NH_3$ and OH exchanging).

Anal. Calcd for $C_{19}H_{32}ClNO_2$: C, 66.75; H, 9.43; Cl, 10.37; N, 4.10. Found: C, 67.03; H, 9.53; Cl, 10.15; N, 4.04.

16β-Amino-5α-androstan-3α-ol-17-one (**8d**).—An aqueous solution of 0.541 g (1.58 mmol) of **8c** was filtered, neutralized with saturated aqueous sodium bicarbonate, and extracted with ether. The ethereal solution was dried (Na_2SO_4), and the ether was evaporated. The residue was recrystallized from ether, cooled in isopropyl alcohol–Dry Ice. There was obtained 0.082 g (17%) of **8d** as yellow needles: mp 178–180° dec; $[\alpha]^{24}D$ +46° (*c* 1.14, absolute C_2H_5OH); ir (KBr) 1620 (NH_2), 1730 (C=O), and 3500 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.82 (s, 3, C-18 or C-19 H), 0.90 (s, 3, C-18 or C-19 H), 1.88 (s, 2, NH_2), 3.15 (bs, 1, C-3 or C-16 H), and 4.05 (bs, 1, C-3 or C-16 H).

Anal. Calcd for $C_{19}H_{31}NO_2$: C, 74.71; H, 10.23; N, 4.59. Found: C, 74.61; H, 10.19; N, 4.35.

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16β-Salicylidenimino-5α-androstan-3α-ol-17-one.—To a solution of 0.507 g (5.07 mmol) of 16β-amino-5α-androstan-5α-ol-17-one (**8d**) in 10 ml of absolute ethanol was added 0.62 ml of absolute ethanol containing 5.08 mmol of salicylaldehyde and 5 mg of *p*-toluenesulfonic acid. After standing for 62 hr at room temperature, the solvent was evaporated and the residue was recrystallized from ethanol–water. There was obtained 0.087 g (42%) of the *N*-salicylidene derivative, mp 179–181°. Two additional recrystallizations of this substance from ethanol–water returned 0.034 g (16%) of yellow platelets: mp 182–184°; $[\alpha]^{24}D$ −70° (*c* 1.00, absolute C_2H_5OH); ir (KBr) 1625 (C=N), 1740 (C=O), and 3540 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.83 (s, 3, C-18 or C-19 H), 0.97 (s, 3, C-18 or C-19 H), 3.69 (m, 1, C-3 or C-16 H), 4.06 (bs, 1, C-3 or C-16 H), 7.12 (m, 4, aromatic H), and 8.42 ppm (s, 1, CH=N).

Anal. Calcd for $C_{26}H_{35}NO_3$: C, 76.24; H, 8.61; N, 3.42. Found: C, 75.79; H, 8.60; N, 3.23.

2,4-Bisoximino-5α-cholestan-3-one (9).—As described for the preparation of **5b**, except that a 16-fold excess of 2-octyl nitrite[50] was used, 5α-cholestan-3-one (**5a**) was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide. The crude product was recrystallized twice from methanol. Recrystallization then from acetone gave **9** (47%) as yellow, microscopic plates: mp 222–223° dec (lit.[23] mp 234–235° dec); $[\alpha]^{25}D$ +138° (*c* 0.751, 1 *N* ethanolic KOH); ir (KBr) 1620 (C=N), 1730 (C=O), and 3200 cm^{-1} (broad, OH).

Anal. Calcd for $C_{27}H_{44}N_2O_3$: C, 72.93; H, 9.97; N, 6.30. Found: C, 72.99; H, 9.86; N, 6.04.

2,4-Bisoximino-17α-methyl-5-androsten-17β-ol-3-one (10).—As described for the preparation of **5b**, except that a fivefold excess of 2-octyl nitrite[50] was used, 17α-methyl-4-androsten-17β-ol-3-one (**16**), mp 164–167°, $[\alpha]^{26}D$ +76° (*c* 1.02, absolute C_2H_5OH) [lit.[59] mp 164°, $[\alpha]D$ +76° (alcohol)], was nitrosated in *tert*-butyl alcohol–potassium *tert*-butoxide. The crude product (17%) was collected by filtration and then was thoroughly washed with acetone. Recrystallization by evaporation of a methanol solution gave **10** (10%) as yellow, microscopic plates: mp >300° dec; $[\alpha]^{27}D$ −7° (*c* 0.502, absolute C_2H_5OH); ir (KBr) 1720 (C=O), 3150 (broad, OH), and 3500 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{28}N_2O_4$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.14; H, 7.64; N, 7.28.

2,5-Diisopropyl-3,6-dimethylpyrazine (11).—An aqueous solution of 5.93 g (39.1 mmol) of **1c** was neutralized with 10% aqueous sodium hydroxide. The solution was extracted with three portions of ether. The combined ethereal solutions were dried (Na_2SO_4). Evaporation of the ether gave 2.56 g of oil which was identified as a mixture of 3-amino-4-methyl-2-pentanone (**18**) and **11**: nmr of **18** (neat) δ 0.66 (d, 6, *J* = 7.0 Hz, C-4 CH_3 and C-5 H), 2.02 (s, 2, NH_2), and 2.17 ppm (s, 3, C-1 H). The oil was redissolved in aqueous sodium hydroxide, and **11** precipitated as white needles, mp 41–44°. Recrystallization of the solid from ethanol–water gave 0.872 g (23%) of **11** as white needles which was sublimed at 25° (0.05 mm): mp 44–46°; ir (KBr) 1430, 1465, and 1480 cm^{-1}; nmr (CCl_4) δ 1.23 [d, 6, *J* = 7.0 Hz, C-2 and C-5 $(CH_3)_2CH$], 2.47 (s, 3, C-3 and C-6 CH_3), and 3.12 ppm [sept, 1, *J* = 7.0 Hz, C-2 and C-5 $(CH_3)_2CH$].

Anal. Calcd for $C_{12}H_{20}N_2$: C, 74.95; H, 10.48; N, 14.57; mol wt, 192.30. Found: C, 74.85; H, 10.40; N, 14.57; mol wt (osmometric in $CHCl_3$), 189.

Di(17β-hydroxy-5α-androstano)[2,3-*b*:2′,3′-*e*]pyrazine (12).—An aqueous solution of 0.431 g (1.26 mmol) of **6c** was neutralized with saturated aqueous sodium carbonate. The solution was extracted with ether. The ethereal solution was dried (Na_2SO_4). Evaporation of the ether gave 0.338 g of residue: ir (KBr) 1670 (strong, C=N) and 1730 cm^{-1} (weak, C=O). The residue was dissolved in absolute ethanol and 0.027 g (0.16 mmol) of *p*-toluenesulfonic acid added. Immediately the solution became dark orange. After 5 min, precipitation of a solid began. It was complete after 0.5 hr. The precipitate was collected by filtration, washed with absolute ethanol, and dried. Thus was obtained 0.259 g (72%) of crude **12**. Recrystallization from chloroform–absolute ethanol gave 0.196 g (54%) of **12** as white needles: mp >300° dec; $[\alpha]^{25}D$ +79° (*c* 0.782, $CHCl_3$); ir (KBr) 1390–1400, 1445, and 3440–3460 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 0.78 (s, 3, C-18 or C-19 H) and 0.82 ppm (s, 3, C-18 or C-19 H); CD ($CHCl_3$) (*c* 0.00626) $[\theta]_{400}$ ±0, $[\theta]_{352}$ ±0, $[\theta]_{328}$ −1300 (max), $[\theta]_{316}$ ±0, $[\theta]_{313}$ +1100 (max), $[\theta]_{311}$ +970 (min), $[\theta]_{310}$ +1800 (max), $[\theta]_{307}$ +1100 (min), $[\theta]_{306}$ +1800 (max), $[\theta]_{303}$ +1300 (min), $[\theta]_{301}$ +1500 (max), $[\theta]_{297}$ +900 (min), $[\theta]_{296}$ +1200 (max), $[\theta]_{295}$ +990 (min), $[\theta]_{294}$ +1700 (sh), $[\theta]_{287}$ +5300 (max), $[\theta]_{263}$ ±0, $[\theta]_{246}$ +4600 (c-off); ORD ($CHCl_3$) (*c* 0.156) $[\phi]_{550}$ +620°, $[\phi]_{440}$ +1100° (c-off); (*c* 0.0156) $[\phi]_{440}$ +1200°, $[\phi]_{314}$ +5600° (pk), $[\phi]_{307}$ +4200° (tr), $[\phi]_{305}$ +4500° (pk), $[\phi]_{303}$ +3800° (tr), $[\phi]_{300}$ +5100° (pk), $[\phi]_{297}$ +4100° (tr), $[\phi]_{295}$ +6000° (pk), $[\phi]_{294}$ +4700° (tr), $[\phi]_{293}$ +6600° (pk), $[\phi]_{291}$ +4200° (tr), $[\phi]_{288}$ +7900° (pk), $[\phi]_{287}$ +5900° (tr), $[\phi]_{286}$ +6800° (pk), $[\phi]_{275}$ +2900° (tr), $[\phi]_{244}$ +16,000° (pk), $[\phi]_{240}$ +13,000° (c-off).

Anal. Calcd for $C_{38}H_{56}N_2O_2$: C, 79.67; H, 9.85; N, 4.89 mol wt, 572.84. Found: C, 79.50; H, 9.60; N, 4.60; mol wt (osmometric in $CHCl_3$), 547.

Di[(1*R*)-bornano][2,3-*b*:2′,3′-*e*]pyrazine (13).—A mixture of 0.560 g (2.75 mmol) of **4c**, water, and carbon tetrachloride was neutralized with 8 ml of 10% aqueous sodium hydroxide. The carbon tetrachloride solution was separated and reduced in volume to 1 ml, all within 25 min. The nmr of this solution showed signals for only (1*R*,3*S*)-3-amino-2-bornanone, δ 0.86 and 0.99 (two s, 6 and 3, respectively, C-8, C-9 and C-10 H), 3.21 (s, 2, NH_2, vanished on exchange with deuterium oxide), and 3.43 ppm (d, 1, *J* = 4.5 Hz, C-3 H). After 1 hr, the ratio of NH_2 protons to total methyl protons dropped from 2:9 to 1:6. After 11.5 hr, the ratio was 1:9. There was no evidence in any of the spectra for signals corresponding to **13**. Rather the final spectrum was that of a mixture of substances which is assumed to be the tautomeric dihydropyrazines. Complete removal of the solvent left a yellow oil. Preparative tlc on silica gel with elution with chloroform separated the mixture into three fractions. The major fraction was isolated and again preparative tlc as before separated it into three fractions with the same R_f values as before.

To a mixture of 2.95 g (9.88 mmol) of the dihydropyrazines formed from (1*R*,3*S*)-3-amino-2-bornanone as outlined above, 35 ml of dioxane, 8 ml of water, and 1.4 ml of concentrated sulfuric acid was slowly added a solution of 3.59 g (52.0 mmol) of sodium nitrite in 15 ml of 33% aqueous dioxane. After addition, the mixture was allowed to stand for 10 min. It was then neutralized with saturated aqueous sodium carbonate and extracted with methylene chloride. The methylene chloride solution was dried (Na_2SO_4), and the solvent removed. The residue was chromatographed on silica gel. Elution with chloroform gave 1.41 g (48%) of crude **13**, mp 154–160°. Recrystallization from ethanol–water returned 1.11 g (38%) of **13** as white needles, mp 159–161°. Sublimation of this solid at 120° (0.005 mm) gave 1.09 g (37%) of **13** as white, irregular, crystalline clusters: mp 159–160° (lit.[39] mp 159.5–160°); $[\alpha]^{24}D$ +66° (*c* 1.02, CH_3OH); ir (KBr) 1445 and 1485 cm^{-1}; nmr (CCl_4) δ 0.58, 0.99, and 1.28 (three s, 3, 3, and 3, respectively, C-8, C-9, and C-10 H), and 2.82 ppm (d, 1, *J* = 4.0 Hz, C-4 H); CD (CH_3OH) (*c* 0.00203) $[\theta]_{360}$ ±0, $[\theta]_{310}$ +5200 (max), $[\theta]_{300}$ +3800 (min), $[\theta]_{293}$ +4100 (max), $[\theta]_{268}$ ±0, $[\theta]_{243}$ ±0, $[\theta]_{225}$ −4400 (max), $[\theta]_{220}$ −2200 (c-off); CD (concentrated H_2SO_4) (*c* 0.00149) $[\theta]_{550}$ ±0, $[\theta]_{380}$ ±0, $[\theta]_{369}$ −8400 (max), $[\theta]_{357}$ ±0, $[\theta]_{337}$ +30,000 (max), $[\theta]_{319}$ +18,000 (min), $[\theta]_{277}$ +44,000 (max), $[\theta]_{247}$ ±0, $[\theta]_{234}$ −27,000 (max), $[\theta]_{210}$ ±0 (c-off); ORD (CH_3OH) (*c* 0.00406) $[\phi]_{400}$ +290°, $[\phi]_{325}$ +4100° (pk), $[\phi]_{310}$ +410° (infl), $[\phi]_{320}$ ±0°, $[\phi]_{287}$ −1800° (tr), $[\phi]_{245}$ ±0°, $[\phi]_{235}$ +180° (infl), $[\phi]_{215}$ +9300° (pk), $[\phi]_{210}$ +5400° (c-off).

Dicyclopentano[*b*,*e*]pyrazine (14).—To a solution of 7.01 g (51.6 mmol) of **2c** in 60 ml of 33% aqueous sodium hydroxide, heated on the steam plate, was added 12 ml of 31% aqueous hydrogen peroxide. Heating was continued until gas evolution ceased. The reaction mixture was cooled and 3.08 g (74%) of crude **14** was collected by filtration. Recrystallization from benzene (Norit) gave 1.96 g (47%) of impure **14** as long, white needles, mp 78–83°. Sublimation of this solid at 75° (0.005 mm) gave **14** as white prisms: mp 89–91°; ir (KBr) 1440 and 1470 cm^{-1}; nmr (CCl_4) δ 2.90 (unsymmetrical t, 2, C-1, C-3, C-5 and C-7 H) and 2.30 ppm (m, 1, C-2 and C-6 H). An analytical sample was prepared by sublimation and then protected from the air.

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.49; mol wt, 160.21. Found: C, 74.85; H, 7.48; N, 17.51; mol wt (osmometric in benzene), 155.

The aqueous filtrate from above was thoroughly extracted with ether, acidified with concentrated hydrochloric acid, and again extracted with ether. These latter ether extracts were combined and dried ($MgSO_4$), and the ether was evaporated. Recrystallization of the residue from benzene (Norite) gave 0.112 g (1.6%) of glutaric acid: mp 91–94°; ir (KBr) identical with that of an authentic sample, mp 92–96°; mmp 95–97°.

Dicyclohexano[b,e]pyrazine[36] (**15**).—Using the procedure outlined above for the preparation of **14**, 2.02 g (13.5 mmol) of **3c** was converted to 0.443 g (35%) of crude **15**. Sublimation of the crude product at 55° (0.005 mm) gave 0.375 g (30%) of **15** as white, irregular, crystalline clusters: mp 107–108° (lit. mp 109.6–110.6[9] and 108–109°);[37] ir (KBr) 1390 and 1435 cm^{-1}; nmr (CCl_4) δ 1.85 (bs, 1, C-2, C-3, C-7, and C-8 H) and 2.78 ppm (bs, 1, C-1, C-4, C-6, and C-9 H).

As above, there was also isolated 0.748 g (38%) of crude acipic acid, mp 138–146°. Recrystallization from benzene gave 0.354 g (18%) of adipic acid: mp 149–153°; ir (KBr) identical with that of an authentic sample, mp 150–154°; mmp 149–156°.

Androstan-17β-ol-2,3-dione Monohydrate (**17**).—Using a procedure described earlier,[25] 0.285 g (0.892 mmol) of **6b** was treated with 3.5 g (0.028 mmol) of sodium sulfite in 15 ml of glacial acetic acid. Isolation of the product in the usual way[25] gave 0.076 g (26%) of crude **17**. Recrystallization from ethanol–water gave 0.027 g (9%) of **17** monohydrate: mp 161–164° dec (lit.[24] mp 232–234°, not hydrated, recrystallized from chloroform); uv max (absolute C_2H_5OH) 270 nm (ϵ 6400); nmr ($CDCl_3$) δ 0.77 (s, 3, C-18 or C-19 H), 1.05 (s, 3, C-18 or C-19 H), 5.71 (d, 0.2, J = 3.0 Hz, C-4 H of **17b**), and 6.39 ppm (s, 0.8, C-1 H of **17a**).

Anal. Calcd for $C_{19}H_{28}O_3 \cdot H_2O$: C, 70.77; H, 9.38; mol wt, 322.43. Found: C, 71.02; H, 9.33; mol wt (mass spectrum), 305 ($M^+ - H_2O + 1$ = 305.42), 304 ($M^+ - H_2O$).

(1*R*,3*S*)-3-Salicylidenimino-2-bornanone (**20**).—To a mixture of 25 ml of water, 25 ml of ether, and 0.498 g (2.44 mmol) of **4c** was added 8 ml of 10% aqueous sodium hydroxide. The layers were separated, and the aqueous layer was extracted with four 25-ml portions of ether. The combined ethereal solutions were washed with water, dried (K_2CO_3), and filtered. To this solution was added 3.5 ml of absolute ethanol containing 2.9 mmol of salicylaldehyde. The solvent was evaporated. The crystalline residue was recrystallized from methanol, and there was obtained 0.313 g (47%) of **20**, mp 103–105°. After sublimation at 90° (0.005 mm), there was obtained 0.285 g (43%) of **20** as yellow platelets: mp 107–108°; $[\alpha]^{25}D$ −170° (*c* 0.828, CH_3OH); ir (KBr) 1630 (C=N) and 1750 cm^{-1} (C=O); nmr (CCl_4) δ 0.91 and 1.01 (two s, 6 and 3, respectively, C-8, C-9, and C-10 H), 3.85 (d, 1, J = 4.5 Hz, C-3 H), 7.01 (m, 4, aromatic H), 8.50 (s, 1, CH=N), and 12.06 ppm (s, 1, OH).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.58; H, 7.82; N, 5.19.

Methyl 16,17-*seco*-5α-Androstan-3β-ol-16-oate-17-oic Acid (**21**).—A 10% excess of 10% aqueous sodium hydroxide was added to a solution of 0.303 g (0.886 mmol) of **7c** in 50 ml of methanol. The mixture was stirred overnight, diluted with water, and then thoroughly extracted with ether. Evaporation of the ether gave only a trace of residue. The aqueous solution was acidified with 2 *N* hydrochloric acid and again thoroughly extracted with ether. This ethereal solution was dried (Na_2SO_4), and evaporation of the ether gave 0.271 g of residue, mp 95–145°. Two recrystallizations of this solid from ethanol–water gave 0.082 g (26%) of **21** as very fine, white needles, mp 189–190°. Sublimation at 150° (0.005 mm) gave **21**: mp 183–184°; $[\alpha]^{22}D$ −90° (*c* 0.36, absolute C_2H_5OH); ir (KBr) 1715 (C=O), 2600 (CO_2H), and 3410 cm^{-1} (OH); nmr ($CDCl_3$) δ 0.78 (s, 3, C-18 or C-19 H), 1.10 (s, 3, C-18 or C-19 H), 1.98 (s, 3, OCH_3), and 4.64 ppm (bs, 2, OH, disappeared on shaking with D_2O); mass spectrum *m/e* (% of base peak, assignment) 352 [11, **22** (M^+)], 278 (23, **24**), 74 (34, **23**).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15; mol wt, 352.46. Found: C, 68.38; H, 9.30; mol wt (mass spectrum), 352.

Registry No.—**1b**, 31571-12-7; **1c**, 5440-22-2; **2b**, 31579-37-0; **2c**, 5464-16-4; **3c**, 6946-05-0; **4a**, 464-49-3; **4b**, 31571-14-9; **4c**, 31638-54-7; **5b**, 31571-15-0; **6a**, 521-18-6; **6b**, 31571-17-2; **6c**, 20985-72-2; **7a**, 481-29-8; **7b**, 31615-29-9; **7c**, 31571-20-7; **8a**, 53-41-8; **8b**, 31571-22-9; **8c**, 31571-23-0; **8d**, 31571-24-1; **9**, 7768-89-0; **10**, 31571-26-3; **11**, 30590-92-2; **12**, 20985-93-7; **13**, 31571-28-5; **14**, 31579-41-6; **15**, 4006-50-2; **17a**, 31571-29-6; **17b**, 31571-30-9; **20**, 31571-31-0; **21**, 31615-30-2; 16β-salicylidenimino-5α-androstan-3α-ol-17-one, 31571-32-1.

Reactions of Amines. XVII. The Oxidation of α-Substituted α-Amino Ketones with Lead Tetraacetate[1,2]

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The oxidation of several α-substituted α-amino ketones with lead tetraacetate (or iodosobenzene diacetate) resulted in cleavage of the molecule between the carbonyl and carbinamine functions, yielding acid derivatives derived from the acyl moiety of the molecule and nitriles derived from the carbinamine moiety. In the presence of an alcohol moderate yields of ester and nitrile were obtained. In the absence of alcohol the yield of cleavage products was lower and acetylation of the amino ketone became a more competitive reaction. The oxidation of 2-amino-3,3-dimethyl-1-indanone (**11**) gave a moderate yield of 1,1-dimethylhomophthalic anhydride presumably derived from an intramolecular of an intermediate such as **12**.

This communication is the fifth[3] in a series directed toward the study of the oxidation of organic nitrogen compounds. Several of the next papers in this series will be concerned with the oxidation of nitrogen analogs of the 1,2-glycols[4] and α-hydroxy ketones[4] in which one or more carbon or oxygen atoms have been replaced by nitrogen. For purposes of later comparisons it is necessary to know first how simple analogs, such as the α-amino ketones, behave toward selected oxidants. In this paper the oxidation of *α-substituted* α-amino ketones with lead tetraacetate and iodosobenzene diacetate is discussed.

On the basis of the known, but imperfectly studied, cleavage of 1,2-amino alcohols to carbonyl compounds and imines (or nitriles) on oxidation with lead tetraacetate (eq 1)[4-6] and the known cleavage of α-hydroxy ketones to carbonyl compounds and acid derivatives with the same reagent (eq 2), it might be expected that

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